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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1653	20

DATE MAILED: 09/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/643,197	DESMAZEAU ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-34* is/are pending in the application.

4a) Of the above claim(s) *31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-30 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 19 (filed 6/23/03), claims 26 and 32 have been amended.

Applicants have argued that they now confirm an election in response to the Office action that was mailed 12/11/01. However, this particular Office action has been superceded by the restriction requirement that was mailed 4/8/02. Accordingly, the election filed 3/11/02 is moot. In addition, an election to the Office action mailed 4/8/02 has already been made of record; no further affirmation of that election is required.

Claims 18-34 remain pending; claim 31 remains withdrawn from consideration.

Applicants arguments filed 6/23/03 have been considered and found not persuasive.

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The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-30, 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is asserted in the specification that the claimed compounds are effective to inhibit growth of bacteria. However, there is no evidence that this is the case. As stated in *Ex parte*

Forman (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, structure/activity relationships of antibacterial compounds are unpredictable. Consider, for example, the following:

- Gavini ("Pyridazine N-oxides. III. Synthesis and in vitro antimicrobial properties of N-oxide derivatives based on tricyclic indeno[2,1- c]pyridazine and benzo[f]cinnoline systems", *Archiv der Pharmazie* **333** (10) 341-6, 2000) discloses the preparation and testing of a series of pyridazine N-oxides. With the exception of compounds 3a, 3b, 4b and 5b, the compounds "demonstrated no activity against bacteria" (page 342, col 2).

- Fudou ("Haliangicin, a novel antifungal metabolite produced by a marine myxobacterium. 1. Fermentation and biological characteristics", *Journal of Antibiotics* **54** (2) 149-52, 2001) discloses the isolation of haliangicin which is produced by a marine bacteria; the compound contains a conjugated tatraene moiety and exhibited no antibacterial activity.

- Juvvadi ("Structure-activity studies of normal and retro pig cecropin-melittin hybrids", *Journal of Peptide Research* **53** (3) 244-51, 1999) discloses the preparation and antibacterial activity of cecropin-melittin hybrid peptides. Also disclosed is that the "retro" analogs (the polarity of the amide bond reversed) lost antibacterial activity.

- Avrahami (*Biochemistry* **40** (42) 12591-603, 2001) studied the effects of amino acid substitutions on the antimicrobial activity of amphipathic antimicrobial peptides. Many of the compounds prepared lost antibacterial activity as a result of a single amino acid substitution. Although after-the-fact rationalizations were provided, the observed structure/ activity relationships could not have been predicted *a priori*.

These and other references disclose that there do exist compounds which exhibit no antibacterial activity, and many of these inactive compounds are structurally analogous to compounds that are active. The key point is that the factors which give rise to activity or inactivity are unknown in the art; and certainly applicants have made no attempt to discuss such factors.

With regard to the "pharmaceutical composition", this term carries with it the implied assertion of therapeutic efficacy. As it happens, *in vitro* efficacy is not necessarily predictive of *in vivo* efficacy. For example, Otvos (*Protein Science* **9** (4) 742-9, 2000) discloses an example of a compound which is active *in vitro* but not *in vivo*. In addition, diseases caused by bacteria can be rather difficult to treat, even under the best of circumstances. Diseases caused by bacteria include the following:

> Anthrax, Bovine Spongiform, Encephalopathy (BSE), Chicken Pox, Cholera, Conjunctivitis, Creutzfeldt-Jakob Disease, Polio, Nosocomial Infections, Otitis Media, Pelvic Inflammatory disease, Plague, Pneumonia, Dengue Fever, Elephantiasis, Encephalitis, Fifth's Disease, Rabies, Rheumatic Fever, Roseola, Rubella, Sexually Transmitted diseases, Helicobacter Pylori, Smallpox, Strep Throat, septicemia, sickle cell anemia, ulcers, Tetanus, Toxic Shock Syndrome, Lassa Fever, Leprosy, Lyme Disease, Typhoid Fever, Measles, Meningitis, Trachoma, Toxoplasmosis, Tuberculosis, Whooping Cough, Yellow Fever

Which of these, exactly, do applicants believe that they can treat? If the patient is afflicted with AIDS (in addition to a bacterial infection), are the claimed compounds effective? In addition, there is the problem of antibiotic resistance. Presumably applicants are aware of this, but if not, the following two articles discuss this matter:

Liu (*Advances in Experimental Medicine and Biology* **455**, 387 1999)

Monroe (*Current Opinion in Microbiology* **3**(5) 496-501, 2000).

Specifically with regard to endotoxin-associated conditions, consider the following: Corriveau C. C. "Antiendotoxin therapies for septic shock" (*Infectious Agents and Disease*, **2** (1) 44-52, 1993) discloses that there have been numerous attempts over the years to treat human septic shock by inhibiting, neutralizing, or clearing endotoxin, and that the results of those attempts support a conclusion of "unpredictability" in the treatment of the same. Accordingly, (a) one cannot predict antibacterial activity merely by viewing a structure, (b) "undue experimentation" would be required to determine which of the claimed compounds will inhibit bacterial growth, and (c) even if it were true that the compounds exhibited antibacterial activity *in vitro*, "undue experimentation" would be required to determine which of the claimed compounds can be used to treat even <u>one</u> disease caused by bacteria, to say nothing of the considerable number of diseases that one would have to test for therapeutic efficacy against.

In response to the foregoing, applicants have pointed to page 7, line 21 (specification) where there is an unsubstantiated assertion that the claimed compounds exhibit antibacterial activity. However, such an unsubstantiated assertion does not constitute evidence. Next, applicants have pointed to page 33, lines 1-11, where it is asserted that if one of the claimed compounds is combined with a prior art compound which other microbiologists have

to exhibit antibacterial activity, the result is that the claimed compound does not eliminate the activity of the prior art compound. However, such a result proves nothing. If a microbiologist combines distilled water with a prior art compound that is known to inhibit growth of bacteria, the result will be that the mixture of water and the compound will also inhibit growth of bacteria. Does this mean that water is effective to inhibit growth of bacteria, even *in vitro*? The fact that an inert compound has no effect on the antibacterial activity of a prior art compound does not mean that the inert compound is itself antibacterial. The results which have been asserted on page 33 are not meaningful at all.

It may turn out, at some point in the future, that applicants will assert that the claimed compounds exhibit some sort of synergystic effect when combined with a known (prior art) antibacterial agent. Should this event come to pass, questions will then be raised about the statistical methods which may have been used. For example, suppose that an investigator has two rats, both infected with *S. aureus*, and two compounds, designated "X" and "Y". Compound "X" has been shown definitively to exhibit antibacterial activity, and compound "Y" is untested, and may be inactive. The researcher then administers compound "X" to the first rat, and a mixture of "X" and "Y" to the second. The result is that the first rat dies, and the second rat lives. In such a case, the result would be meaningless for a variety of reasons, including the sample size. If applicants are unaware that artifacts in statistical analysis are common, it is suggested that applicants review each of the following references:

Ludbrook (*Clinical and Experimental Pharmacology and Physiology* **28** (5-6) 488-92, 2001)

Bryant (*Pediatric Allergy and Immunology* 9 (3) 108-15, 1998)

Bezeau (*Journal of Clinical and Experimental Neuropsychology* 23 (3) 399-406, 2001)

Bolton (*Journal of Clinical Pharmacology* 38 (5) 408-12, 1998)

Willenheimer (*Progress in Cardiovascular Diseases* 44 (3) 155-67, 2001)

Chung (*Plastic and Reconstructive Surgery* 109 (1) 1-6, 2002)

Atkinson (*Chronobiology International* 18 (6) 1041-53, 2001).

Next, applicants have implied that if the label "streptogramin" is applied to a compound, the application of such a label converts an inactive compound into an active one. However, this is not the case. The reality in microbiology is that minor structural changes can eliminate activity, and moreover, one cannot predict which structural changes will increase activity, which structural changes will decrease activity, and which structural changes will be ~~begign~~ benign.

Next, applicants have allowed that perhaps within the scope of the claimed genus there are a few inoperative embodiments. While this is no doubt true, the fact of a few inoperative embodiments is not the principle basis of this rejection. This rejection holds that the genus as a whole is not enabled, and not merely that the scope is too broad. The issue

of scope need not be discussed any further, at least not until such time that applicants provide evidence that at least one compound within the entire genus exhibits some degree of antibacterial activity. This has not been done. Applicants have only asserted that the claimed compounds fail to extinguish the antibacterial activity of known prior art compounds. However, this does not amount to a showing of antibacterial activity.

Next, applicants have pointed to *In re Brana*, and have argued that the CAFC reversed a rejection of claims drawn to treatment of diseases. It is the examiner's position that applicants are incorrect on this point. However, this matter can be settled by identifying, by claim number, the specific claim of USP 5,552,544 which is drawn to treatment of a disease, or to a pharmaceutical composition (*per se*). After this claim number has been identified, the discussion regarding Brana can be resumed.

On page 11 of the response (paper No. 19), applicants have argued that the claimed compounds exhibit *in vivo* activity, and have pointed to page 33, line 5+. However, such an assertion is contrary to what is stated in the specification at page 33, line 5+, and contrary also to what applicants have stated on page 8 of the response (paper No. 19). What is stated in the specification is that a mixture which contains **both** a claimed compound and a proven (prior art) antibacterial agent will exhibit antibacterial antibacterial activity. This result, however, is entirely consistent with the claimed compounds being inactive.

Next, applicants have pointed to Brana on page 11 of the response. As indicated above, the application of Brana matured into USP 5,552,544. Applicants are again requested to

identify by claim number the claim of USP 5,552,544 which is drawn to a pharmaceutical composition, or to treatment of a disease. In any case, Brana did provide *in vitro* data on the claimed compounds. Brana did not simply combine inert compounds with known anticancer agents.

Next, applicants have implied that the examiner has required human clinical data. However, the examiner has imposed no such requirement.

It remains the case that "undue experimentation" would be required to determine which, if any, of the claimed compounds can exhibit antibacterial activity (when not combined with a known antibacterial agent). It is suggested that applicants provide at least *in vitro* data that establishes the bacterial growth inhibitory efficacy that has been asserted; also suggested is that the term "pharmaceutical" be deleted from whichever claims recite it.

*

Claim 33 is rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 makes reference to various group A streptogramin derivatives such as pristinamycin II_B. However, this renders the claim indefinite. It is suggested that a chemical name or structure be provided for each of the listed compounds.

*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600